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NeoSep1: a study to determine the ranking of existing and new antibiotics combinations to treat newborn babies who are in hospital with severe sepsis

Submission date
17/01/2022

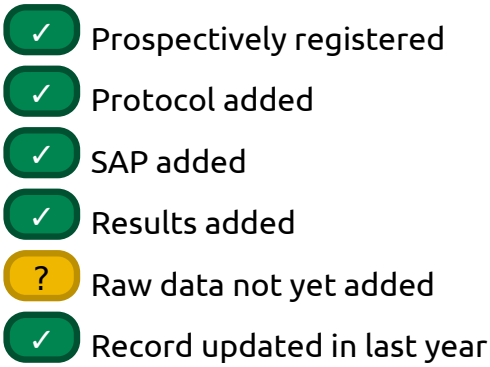
Recruitment status
Recruiting

Registration date
24/02/2022

Overall study status
Ongoing

Last Edited
10/06/2024

Condition category
Infections and Infestations



Plain English Summary
Background and study aims
At present, babies who are admitted to hospital with sepsis are treated with medicines called “antibiotics”. In many countries, these antibiotics are those recommended by the World Health Organisation (WHO). Other countries use different antibiotics based on local policies but unfortunately, these are not always easily available. The use of different antibiotics also varies from baby to baby and between countries and hospitals.

More and more infections are being caused by bacteria that are “resistant” to commonly used antibiotics; this means these antibiotics will not kill the bacteria and therefore will not cure the infection. These bacteria are often called multidrug-resistant, as they are not killed by most antibiotics. We need to find new ways of treating these infections, and using combinations of existing antibiotics is one possibility. Fosfomycin, flomoxef, and amikacin are three antibiotics that could be combined into different two-drug regimens. Another option is to give stronger antibiotics at the start of treatment. The problem with doing this is that not all babies will need these stronger antibiotics, and the more we use them, the more resistance will develop to these antibiotics. So using them in lots of babies now, who don’t all need them, may mean that in the future we will not be able to use them in any babies who might need them.

The NeoSep1 study will test how well giving fosfomycin and amikacin, flomoxef and amikaci, or fosfomycin and flomoxef works to treat babies 28 days old or younger who are in hospital with severe sepsis. It will also test how well other antibiotics or combinations of antibiotics work.

Who can participate?
Over 3,000 babies aged 28 days old or younger who are in hospital with severe sepsis will be included in Part 1 and 2 of the NeoSep1 study. Participants will be recruited from all over the world, and in particular from low and middle-income countries such as South Africa, Kenya, and other countries in Africa and South East Asia.

What does the study involve?
The study will be divided into two parts: Part 1 and Part 2.

Part 1 will measure the level of fosfomycin, amikacin, and flomoxef in the baby's blood; this is called a pharmacokinetic study or PK study. Each baby will get one of the three new combinations of antibiotics: fosfomycin and amikacin, flomoxef and amikacin, or fosfomycin and flomoxef. We will study 20 babies in each group, one after the other. We will use doses recommended in other studies. The information collected for Part 1 will confirm how much fosfomycin and/or flomoxef we should use in the next part of the study. We will also collect data on any side effects. Babies in Part 1 will be followed up for 28 days.

In Part 2 of the study, we will check how well these three combinations, as well as other antibiotics that are used routinely to treat sepsis in newborn babies, treat bacterial infections, and stop babies from dying.

Babies will get antibiotics for approximately 7-10 days in the first instance (their "first line" treatment). If a baby's condition gets worse during this time or doesn't get better as would be expected, doctors will be able to give them a different antibiotic (also known as "second-line" treatment) to see if they do better with a different antibiotic. Babies in Part 2 will be followed up for 90 days, with a visit or telephone call 28 and 90 days after the baby entered the study to see if the baby is still doing well.

What are the possible benefits and risks of participating?
Participating in this study may not directly benefit the babies taking part, but the information we get from the study will help us work out the best available treatment combinations to treat babies with sepsis in the future. While in hospital, babies taking part in the study will be reviewed daily by the study clinicians and nurses, together with the regular hospital staff.

Where is the study run from?
Global Antibiotic Research & Development Partnership (Switzerland)

When is the study starting and how long is it expected to run for?
From August 2022 to December 2028

Who is funding the study?
Global Antibiotic Research & Development Partnership (Switzerland)

Who is the main contact?
Ms Nathalie Khavessian
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Contact information

Type(s)
Public

Contact name
Ms Nathalie Khavessian

Contact details

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Type(s)
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Protocol/serial number
v1.0

Study information

Scientific Title
An open-label randomised controlled trial comparing novel combination and existing antibiotic regimens for the empiric treatment of neonatal sepsis with a run-in confirmatory pharmacokinetic phase (NeoSep1)

Acronym

NeoSep1

Study hypothesis
Part 1:
Recommended doses of fosfomycin and floxomef, in combinations to be studied in Part 2, will provide adequate drug levels in neonates with sepsis.

Part 2:
Mortality in hospitalised neonates with sepsis can be reduced by choosing a top-ranked antibiotic regimen compared with the WHO recommended empiric antibiotic regimens for neonatal sepsis and other currently used regimens.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 31/08/2022, Stellenbosch University Health Research Ethics Committee (Stellenbosch University, Private Bag X1, Matieland, 7602, Stellenbosch, South Africa; +27 021 938 9075; blanchep@sun.ac.za), ref: M22/05/007
2. Approved 15/08/2022, University of the Witwatersrand Human Research Ethics Committee (Medical) (Suite 189, Private Bag x2600, Houghton 2041, South Africa; +27 11 274 9200; HREC-Medical.ResearchOffice@wits.ac.za), ref: 220509B
3. Approved 27/07/2022, Research Ethics Committee of Kenya Medical Research Institute (Scientific and Ethics Review Unit, P.O Box 54840 00200 off Mbagathi Road, Nairobi, Kenya; +254 0717 719 477; seru@kemri.org), ref: KEMRI/RES/7/3/1
4. Approved 02/08/2022, South African Health Products Regulatory Authority (SAHPRA) (Building A, Loftus Park, 2nd Floor, Kirkness Rd, Arcadia 0083, South Africa; +27 012 501 0413; enquiries@sahpra.org.za), ref: 20220614
5. Approved 21/12/2022, Pharmacy and Poisons Board (PPB) (Lenana Road, P.O. Box 27663-00506, Nairobi, Kenya; +254 709 770 100; info@pharmacyboardkenya.org), ref: PPB/ECCT/22/08/03/2022(335)

Study design
Phase II/III multicentre personalized randomized controlled trial (PRACTical) incorporating a Sequential Multiple Assignment Randomised Trial (SMART) design

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Condition
Neonatal sepsis

Interventions
Randomisation:
Treatment allocation (Part 1 only): Run-in sequential treatment cohort:
1. Fosfomycinand amikacin
2. Flomoxef and amikacin
3. Flomoxef andfosfomycin

Randomisation (Part 2 only): The main empiric treatment trial (Part 2) will use a novel tailored randomised controlled trial (PRACTical) design, in which each neonate is randomised to pre-defined first-line regimens that are considered clinically acceptable for that specific site and neonatal sub-population. The design will also incorporate a Sequential Multiple Assignment Randomised Trial (SMART) design to allow randomisation to second-line treatment where indicated. For the second randomisation, personalised randomisation lists will be determined by the neonate's first randomised regimen and what is clinically appropriate for that specific site.

Dosing:
Dosing will depend on the treatment regimen given at enrolment (part 1) or randomisation (part 2). The following provides a summary on the proposed dosing
1. Amikacin: 15 mg/kg total daily dose for sepsis; 15 mg/kg total daily dose for suspected /confirmed meningitis
2. Ampicillin/amoxicillin: 100-150 mg/kg total daily dose for sepsis; 200-400 mg/kg total daily dose for suspected/confirmed meningitis; 2-3 divided doses per day
3. Benzylpenicillin: 100,000-200,000 IU/kg total daily dose for sepsis; 100,000-200,000 IU/kg total daily dose for suspected/confirmed meningitis; 2-4 divided doses per day
4. Cefotaxime: 100-150 mg/kg total daily dose for sepsis; 150-200mg/kg total daily dose for suspected/confirmed meningitis; 2-3 divided doses per day
5. Ceftazidime: 100-150 mg/kg total daily dose for sepsis; 100-150 mg/kg total daily dose for suspected/confirmed meningitis; 3 divided doses per day
6. Ceftriaxone: 80-100 mg/kg total daily dose for sepsis; 80-100 mg/kg total daily dose for suspected/confirmed meningitis; 1-2 divided doses per day
7. Cloxacillin: 100-150 mg/kg total daily dose for sepsis; 100-150 mg/kg total daily dose for suspected/confirmed meningitis; 2-3 divided doses per day
8. Flomoxef: 120-150 mg/kg total daily dose for sepsis; 120-150 mg/kg total daily dose for suspected/confirmed meningitis; 2-3 divided doses per day
9. Fosfomycin: 200-300 mg/kg total daily dose for sepsis; 200-300 mg/kg total daily dose for suspected/confirmed meningitis; 2 divided doses per day
10. Gentamicin: 5-7 mg/kg total daily dose for sepsis; 5-7 mg/kg total daily dose for suspected /confirmed meningitis; 1 divided doses per day
11. Meropenem: 60 mg/kg total daily dose for sepsis; 80-120 mg/kg total daily dose for suspected/confirmed meningitis; 3 divided doses per day
12. Piperacillin/tazobactam: 240-300 mg/kg (piperacillin) total daily dose for sepsis total daily dose for suspected/confirmed meningitis; 3-4 divided doses per day

Treatment:
Part 1: Planned duration of treatment at enrolment for culture-negative is to Day 7±2 days, for culture-positive is to Day 10 [-3,+4 days] if there is no switch. If antibiotics are switched, the total planned duration of antibiotic treatment including first and second-line treatment is 14 ±7 days depending on the baby's condition.

Part 2: Planned duration of treatment at enrolment for culture-negative is Day 7±2 days, for culture-positive is Day 10 [-3,+4] days if there is no switch. If antibiotics are switched the total duration of antibiotic treatment including first and second-line treatment is 14 ±7 days depending on the baby's condition.

Assessments:
Assessments (Part 1): PK assessment on Day 1 and Day 5; Clinical assessment on Day 1, Day 5, Day 7, Day 14, and Day 28
Assessments (Part 2): Clinical assessments on Day 3, Day 7, Day 14, Day 28, and Day 90

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Ampicillin and gentamicin, cefotaxime or ceftriaxone, fosfomycinand amikacin, flomoxef and amikacin, ceftazidime, piperacillin/tazobactam, piperacillin/tazobactamand amikacin, meropenem

Primary outcome measure
Part 1:
1. PK parameters derived for fosfomycin and flomoxef using the population PK model using Day 1 PK samples taken at 5 min, 30 min, and 4 h post-treatment or 15 min, 1 h, and 6 h post-treatment from the population:
1.1. Clearance (CL)
1.2. Central volume of distribution (V)
1.3. Postnatal maturation function parameters: fraction of size and scaled clearance at birth (Fm) and the rate of postnatal maturation of clearance (Km)

Part 2:
1. 28-day mortalitymeasured from patient records at 28 days

Secondary outcome measures
Part 1:
1. PK parameters derived for fosfomycin and flomoxef using the population PK model using PK samples taken on Day 1 and Day 5:
1.1. Maximum plasma concentration (Cmax)
1.2. Time to Cmax (Tmax)
1.3. Apparent terminal elimination half-life (t1/2)
1.4. Area under the plasma concentration-time curve from 0 to last observed time point (AUC0–last)
1.5. Area Under the Curve to infinity (AUC(0–∞))
1.6. Volume of distribution at steady state (Vss)
2. Potential PK/PD relationships using PK and PD samples taken on Day 1 and Day 5:
2.1. Free drug AUC ratio to Minimum Inhibitory Concentration (MIC) (fosfomycin)
2.2. Fraction of time for free concentration above MIC (flomoxef)
3. Safety measured using the following:
3.1. Incidence of Grade 3/4 adverse events (AEs) based on the International Neonatal Consortium Neonatal Adverse Event Severity Scale (NAESS) measured from patient records

between baseline and 28 days
3.2. Incidence of AEs of any grade related toantibiotics measured from patient records throughout the study
3.3. Modification of antibiotics for adverse reactions measured from patient records throughout the study

Part 2:
1. Efficacy measured using the following:
1.1. Clinical status measured using a clinical recovery score based on data from the NeoOBS observational study (NeoSep Recovery Score) at 3, 7, 14, and 28 days after randomisation
1.2. Clinically appropriate need for additional antibiotics beyond the first randomised treatment measured from patient records between the first randomised treatment and the end of the study
1.3. Clinically appropriate need for additional antibiotics beyond the first randomised and second (for failure) treatment measured from patient records between the second randomised treatment and the end of the study
1.4. Cure, defined as clinical improvement and no need for further antibiotic treatment for the original sepsis episode, measured using clinical assessment at the test of cure (TOC) visit (Day 14 ±3 days after randomisation)
1.5. Length of stay during the indexhospitalisation measured from patient records between hospital admission and discharge
1.6. Systemic antibiotic exposure (days on antibiotics) during the indexhospitalisation measured from patient records between hospital admission and discharge
1.7. 90-day mortality measured from patient records at 90 days
1.8. Change in C-reactive protein at baseline, 3, and 7 days (selected sites based on availability)
2. Safety measured using the following:
2.1. Incidence of Grade 3/4 adverse events (AEs) based on the International Neonatal Consortium Neonatal Adverse Event Severity Scale (NAESS) measured from patient records between baseline and 28 days
2.2. Incidence of AEs of any grade related toantibiotics measured from patient records throughout the study
2.3. Modification of antibiotics for adverse reactions measured from patient records throughout the study

Overall study start date
29/04/2021

Overall study end date
31/12/2028

Eligibility

Participant inclusion criteria
1. Currently admitted to hospital
2. Aged ≤28 days (post-natal age)
3. Weight >1000 g
4. Clinical diagnosis of a new episode of sepsis together with planned treatment with IV antibiotics
5. At moderate to high risk of death from this episode of sepsis, based on a neonatal sepsis severity score (NeoSep Severity Score) developed using baseline clinical information and subsequent mortality from the NeoOBS study; specifically, a baseline assessment NeoSep

Severity Score of 4 or higher
6. Can receive at least 2 of the potential treatment options, ensuring randomisation is possible (Part 2 only)
7. IV antibiotics about to be started or not received >24 h of IV antibiotics for this episode of neonatal sepsis at the point of randomisation
8. Parent/guardian willing and able to provide consent (written or, if their baby is severely ill, verbal consent confirmed by written consent as soon as possible). Verbal consent allows for the administration of first-line antibiotics at no or minimal delay.

Participant type(s)
Patient

Age group
Neonate

Upper age limit
28 Days

Sex
Both

Target number of participants
3,060

Participant exclusion criteria
1. A serious, non-infective co-morbidity including major congenital abnormalities (other than prematurity), anticipated to cause death within this admission
2. Previously enrolled in this trial
3. Current participation in any other clinical study of an Investigational Medicinal Product (IMP) that is a systemic drug, unless it has received prior approval by the NeoSep1 Trial Management Group (TMG)
4. Known contraindication to any of the trial antibiotics on the randomisation list for the relevant neonatal sub-population in that site

Recruitment start date
07/03/2023

Recruitment end date
03/06/2027

Locations

Countries of recruitment
Brazil

Congo, Democratic Republic

India

Kenya

Pakistan

South Africa

Switzerland

Uganda

Study participating centre
Tygerberg Children's Hospital
University of Stellenbosch
Francie Van Zijl Avenue
Parow
Western Cape
Cape Town
South Africa
7505

Study participating centre
Chris Hani Baragwanath Academic Hospital
26 Chris Hani Rd
Diepkloof
319-Iq
Johannesburg
South Africa
1860

Study participating centre
KEMRI/Wellcome Trust Research Programme
PO Box 230-80108
Kilifi
Kenya
-

Sponsor information

Organisation
Global Antibiotic Research & Development Partnership

Sponsor details
15 Chemin Camille-Vidart (formerly Chemin Louis-Dunant)
Geneva

Switzerland
1202
+41 22 555 19 90
contact@gardp.org

Sponsor type
Charity

Website
https://gardp.org/

ROR
https://ror.org/0284j4180

Funder(s)

Funder type
Charity

Funder Name
Global Antibiotic Research & Development Partnership

Results and Publications

Publication and dissemination plan
A clinical trial report will be prepared by the Sponsor with input from investigators as appropriate. One copy of the final trial report must be dated and signed by the Sponsor's medical monitor, principal investigators, trial statistician and the clinical trial manager before being transmitted to the regulatory authorities and local ethics committees if required.
A publication policy will be drafted reflecting the following principles:
1. All parties including GARDP, MRC CTU, SGUL, Penta, and participating sites will contribute to the preparation of publication
2. Upon trial completion and finalisation of the trial report, the results of the trial will be submitted for publication to a peer-reviewed journal and posted in a publicly accessible database of clinical trial results
3. Authorship of any publication will be based on the uniform requirements for manuscripts submitted to biomedical journals as defined by the International Committee of Medical Journal Editors (ICMJE)
4. The PK and safety data from Part 1 will be published separately from Part 2, both in a peer-reviewed journal.

Intention to publish date
31/12/2029

Individual participant data (IPD) sharing plan

The contact details for data release requests are Sally Ellis, Childrens Antibiotics Project Leader (+41 22 9077612, sellis@gardp.org). The data sharing policy will be summarised in the study protocol. We intend to make the protocol available via the registry in due course, providing clarification on the details of individual participant data (IPD) sharing.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.0	04/04/2022	12/04/2023	No	No
Statistical Analysis Plan	version 1.0	08/06/2023	29/05/2024	No	No
Poster results	Part 1 results	30/04/2024	10/06/2024	No	No